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Date of Deposit: June 30, 2000

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PATENT
Attorney's Ref. No. 22-55372

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box PATENT APPLICATION
TO THE ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Transmitted herewith for filing is the continuing patent application of:

Inventor(s): Robert B. Rieveley

For: METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES

Enclosed are:

- ☒ 14 pages of specification, 5 pages of claims, and an abstract
- ☒ 3 pages of an Oath or Declaration
  - ☒ A copy of oath or declaration filed with the prior application (37 C.F.R.§ 1.63(d))
- ☒ Associate Power of Attorney.
- ☒ Preliminary Amendment
- ☒ Information Disclosure Statement.
- ☒ Form PTO-1449.

Continuing Application
- ☒ Divisional
  Prior Application Number 08/804,903
  Examiner K. Weddington
  Group/Art Unit 1614

Small Entity Status:
- a. ☐ A small entity statement is enclosed if (b) does not apply
- b. ☒ A small entity statement was filed in the previous non-provisional application and such status is still proper and deserved.

FILING FEE

For	Claims Filed	Number Allotted		Number Extra	Rate	Basic Fee $345.00
Total Claims	24	20	=	4	$9.00	$ 36.00
Independent Claims	6	3	=	3	$39.00	$ 117.00
Multiple Dependent Claim Fee					$130.00	
TOTAL FILING FEE						$498.00

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☒ A check in the amount of $498.00 to cover ☒ filing fee and ☐ assignment recordal fee is enclosed.

☒ The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference herein.

☒ The Commissioner is hereby authorized to charge any additional fees which may be required in connection with the filing of this application and recording any assignment filed herewith, or credit over-payment, to Account No. 02-4550. A copy of this sheet is enclosed.

☒ Please return the enclosed postcard to confirm that the items listed above have been received.

Respectfully submitted,

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cc: Docketing Secretary

Applican r Patentee: Robert B. Rieveley
Serial o Patent No.: _____ Attorney's Docket No.: C413 0005
Filed or Issued: _____
For: METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 C.F.R. 1.9(f) and 1.27(b)) -- INDEPENDENT INVENTOR

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 C.F.R. 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES described in:

[X] the specification filed herewith
[ ] application Serial No. _____ filed _____
[ ] Patent No. _____ issued _____

I have not assigned, granted, conveyed or licensed, and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 C.F.R. 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 C.F.R. 1.9(d) or a non-profit organization under 37 C.F.R. 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey or license, any rights in the invention is listed below:

[X] no such person, concern or organization
[ ] persons, concerns or organizations listed below*

* NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 C.F.R. 1.27)

FULL NAME _____
ADDRESS _____
[ ] Individual [ ] Small Business Concern [ ] Non Profit Organization

FULL NAME _____
ADDRESS _____
[ ] Individual [ ] Small Business Concern [ ] Non Profit Organization

FULL NAME _____
ADDRESS _____
[ ] Individual [ ] Small Business Concern [ ] Non Profit Organization

I acknowledge my duty to file, in this application, or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Robert B. Rieveley		
Name of Inventor	Name of Inventor	Name of Inventor
Inventor's Signature	Inventor's Signature	Inventor's Signature
Feb 20, 1997		
Date	Date	Date

PATENT
Attorney's Matter No. 22-55372

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Rieveley

Art Unit:

Application No.:

Filed: Herewith

For: METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES

Examiner:

Date: June 30, 2000

CERTIFICATE OF MAILING

I hereby certify that this paper and the documents referred to as being attached or enclosed herewith are being deposited with the United States Postal Service on June 30, 2000 as First Class Mail in an envelope addressed to BOX PATENT APPLICATION, ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D C. 20231.

William D Noonan

William D Noonan, M D.
Attorney for Applicant

BOX PATENT APPLICATION
ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

PRELIMINARY AMENDMENT

Before calculating the filing fee, please enter the following amendment in the accompanying patent application:

In the Specification:

Please add the following priority claim on the first page of the specification, immediately after the title:

-- CROSS-REFERENCE TO RELATED APPLICATION

This application is a division of Application No. 08/804,903, filed February 24, 1997, which is incorporated herein by reference. --

In the Claims:

Please cancel claims 1-29 inclusive, without prejudice.

Please add new claims 30 - 53 as follows:

30. A method for the treatment of diabetes mellitus, comprising administering to a person afflicted with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of a sulfonylurea, a biguanide, or an alpha-glucosidase inhibitor.

31. The method of claim 30, comprising administering an insulin sensitizer and a sulfonylurea.

32. The method of claim 30, comprising administering an insulin sensitizer and a biguanide.

33. The method of claim 30, comprising administering an insulin sensitizer and an alpha-glucosidase inhibitor.

34. The method of claim 30, further comprising adding a pharmaceutical carrier to the therapeutically effective amount of the sulfonylurea, the biguanide, or the alpha-glucosidase inhibitor.

35. A composition for the treatment of diabetes mellitus comprising:

(a) a therapeutic amount of an insulin sensitizer; and

(b) a therapeutic amount of a sulfonylurea, a biguanide, or an alpha-glucosidase inhibitor.

36. A composition for the treatment of diabetes mellitus in a mammal comprising:

(a) a therapeutically effective amount of a sulfonylurea; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of the sulfonylurea.

37. The composition of claim 36, further comprising a pharmaceutically acceptable carrier.

38. The composition of claim 36 where the insulin sensitizer is present in the composition in the range of about 10 μg to 10 mg.

39. A composition as claimed in claim 36 wherein the insulin sensitizer is selected from the group consisting of BRL-49653, Pioglitazone HCL, Troglitazone, MC 555, ALRT 268, LGD 1069, Chromic Picolinate, V-411, Vanadyl Sulfate, and Chromic Polynicotinate.

40. A composition for the treatment of diabetes mellitus in a mammal comprising:

(a) a therapeutically effective amount of a biguanide; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of the biguanide.

41. The composition of claim 40, further comprising a pharmaceutically acceptable carrier.

42. The composition of claim 40 where the insulin sensitizer is present in the composition in the range of about 10 μg to 10 mg.

43. A composition as claimed in claim 40 wherein the insulin sensitizer is selected from the group consisting of BRL-49653, Pioglitazone HCL, Troglitazone, MC 555, ALRT 268, LGD 1069, Chromic Picolinate, V-411, Vanadyl Sulfate, and Chromic Polynicotinate.

44. The composition of claim 40 where the biguanide is glucophage.

45. A composition for the treatment of diabetes mellitus comprising:

(a) a therapeutically effective amount of an alpha-glucosidase inhibitor; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of the alpha-glucosidase inhibitor.

46. The composition of claim 45, further comprising a pharmaceutically acceptable carrier.

47. The composition of claim 45 where the insulin sensitizer is present in the composition in the range of about 10 μg to 10 mg.

48. A composition as claimed in claim 45 wherein the insulin sensitizer is selected from the group consisting of BRL-49653, Pioglitazone HCL, Troglitazone, MC 555, ALRT 268, LGD 1069, Chromic Picolinate, V-411, Vanadyl Sulfate, and Chromic Polynicotinate.

49. A method for the treatment of diabetes mellitus comprising administering to a person afflicted with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of an orally ingestible anti-diabetic agent, where

(1) the insulin sensitizer is selected from the group consisting of: BRL-49653, Pioglitazone HCL, Troglitazone, MC 555, ALRT 268, LGD 1069, Chromic Picolinate and V-411; and

(2) the anti-diabetic agent is selected from the group consisting of: a sulfonylurea; a biguanide; and an alpha-glucosidase inhibitor.

50. The method of claim 49, wherein the insulin sensitizer is V-411.

51. The method of claim 49, wherein the anti-diabetic agent is a biguanide.

52. The method of claim 49, wherein the anti-diabetic agent is a sulfonylurea.

53. The method of claim 49, wherein the anti-diabetic agent is an alpha-glucosidase inhibitor.

REMARKS

By this preliminary amendment, claims 1-29 are canceled without prejudice, and new claims 30-53 are added.

New claims 30-53 are supported by the specification as filed. In particular, support can be found in the claims as originally filed (pages 15 through 19) and the summary of the invention (pages 8 and 9).

All new claims are fully supported by the specification. No new matter has been added by this preliminary amendment.

Respectfully submitted,

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METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES

TECHNICAL FIELD OF THE INVENTION

This invention is directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II). More specifically, this invention pertains to a novel method of and compositions for orally treating diabetes mellitus by administering to a person afflicted with diabetes mellitus one or more sensitizer chemicals, which increase the cells ability to utilize glucose, along with orally ingested medications for the treatment of diabetes mellitus.

BACKGROUND OF THE INVENTION

It is estimated that 1.5 to 2% of the entire population of the world suffers from diabetes mellitus of some type. Diabetes mellitus is a chemical disorder of the human body primarily involving an inability of the body to properly utilize sugar and other chemical compounds in the metabolism of the body. It is characterized by an elevation in the concentration of sugar in the blood and also by the appearance of sugar in the urine.

In general terms, diabetes mellitus is classified into three types, namely, Type I, IGT and Type II. In Type I diabetes, the beta cells in the pancreas, probably through an auto-immune reaction, cease producing insulin into the bloodstream of the person. Insulin is a chemical substance which is normally secreted into the bloodstream by beta cells within the pancreas. Insulin is vitally important to the person because it enables the person to properly utilize and consume sugar in the bloodstream as part of the metabolism process.

In Type I cases, where the pancreas has ceased producing insulin, it is necessary for the afflicted person

to inject insulin directly into the bloodstream at prescribed periodic intervals and dosages in order to control the level of sugar in the blood. This is called intravenous injection. Oral ingestion of insulin is also possible but usually less effective due to the degradation of insulin caused by the passage through the stomach and upper intestine.

In IGT and Type II diabetes, the pancreas continues to produce insulin but, some or all of the insulin may fail to bind to the body's cell receptors and/or internalization of insulin in the cells is reduced. In such cases, there may be a sufficient level of insulin in the blood, but the ability of the cells to uptake glucose is reduced or non-existent because of reduced internalized insulin.

The existence of Type I, IGT or Type II diabetes in a person is usually determined by an oral glucose tolerance test (OGTT). OGTT is a test in which the fasting patient is given a known amount of glucose (sugar) by mouth, and the blood is tested at intervals thereafter to note the quantity of sugar in the blood. A curve is then constructed from which important information about the person can be drawn. The glucose tolerance test curve will typically show whether the patient is hyperglycaemic (diabetic) or whether the patient has too little sugar in his or her blood and is therefore hypoglycaemic.

Symptoms of hyperglycaemia can be headaches, increased urination, thirst, nausea, weight loss, fatigue and coma. Hyperglycaemia can be caused by Hypoinsulinism, a condition in which the insulin producing beta cells of the pancreas fail to manufacture insulin or manufacture and secrete a reduced amount of insulin into the bloodstream. In such cases, levels of sugar in the blood are dramatically increased.

Hyperglycaemia can also be caused by failure of some or all of the available insulin in the blood to bind to the body's cell receptors and/or internalization of insulin in the cells is reduced.

Hypoglycaemia (too little sugar) is also a blood condition that diabetics must constantly guard against. The symptoms of hypoglycaemia are abrupt episodes of intense hunger, trembling of the hands and body, faintness, black spots before the eyes, mental confusion, sweating, abnormal behaviour, and, in severe cases, convulsions with loss of consciousness. In such cases, examination of the blood at the time of these attacks will show an extremely low level of circulating sugar in the blood.

Hypoglycaemia can be caused by Hyperinsulinism, a condition in which the insulin producing beta cells of the pancreas manufacture and secrete an excessive amount of insulin into the bloodstream. Levels of sugar in the blood are therefore dramatically reduced.

Transfer of glucose from the blood stream to the body cells is believed to be enabled by the binding of insulin to the cell receptors. Receptor bound insulin then increases the amount of insulin that is internalized in the cell. Internalized insulin results in increased utilization of glucose in the cell and consequently increased metabolism. A drug that sensitizes the surface of a body cell to increase the cell's internalization of insulin or is believed or purported to function by sensitizing a cell to insulin is known herein as an "insulin sensitizer".

The following is a list of drugs that are being or have been tested as insulin sensitizers:

1. *BRL-49653* as produced by SmithKine Beecham or by some other advocate.

2. *Pioglitazone HCL* as produced by Takeda or some other advocate.

3. *Troglitazone, Noscal* or *Resiline* as produced by Sankyo, Glaxo Wellcome or Warner-Lambert.

4. MC 555 as produced by Mitsubishi or some other advocate.

5. ALRT 268 as produced by Ligand or some other advocate.

6. LGD 1069 as produced by Ligand or some other advocate.

7. Chromic Picolinate.

8. Diab II™ (otherwise known as V-411) or Glucanin and produced by Biotech Holdings Ltd. or Volque Pharmaceutical.

Intravenous injection is the anathema of all Type I and II diabetics forced to inject insulin. These diabetics today are cursed to a lifelong ritual of having to inject insulin into their bloodstream, usually several times a day, in order to keep the level of insulin in the blood within prescribed levels.

Considerable research is being conducted to develop an insulin which can be orally ingested for the treatment of Type I or II diabetes. Such an orally ingestible insulin would be welcomed by Type I and Type II diabetics because it would no longer be necessary for them to undergo a daily routine of intravenous insulin injections. Unfortunately, to date, an orally ingested insulin has not yet been successfully developed.

A major problem is that stomach acids and gut enzymes of the person destroy most of the orally ingested insulin and hence the amount of ingested insulin that reaches the bloodstream is less than what is therapeutically required for the diabetic to function normally. Time release systems, which protect the insulin while it passes through the stomach and upper intestine, and release the insulin subsequently, are being researched to alleviate this problem. The theory of these time release systems is to incorporate the insulin with appropriate time release mechanisms so the insulin is not released until after the time release-insulin combination has passed through the stomach and the preliminary stages of the digestive process.

IGT and Type II Diabetes can be treated with one or more classes of drugs generally known as hypoglycaemics to reduce blood glucose levels.

One class of hypoglycaemics are known as "sulfonylureas". Trade-marks for commercially available sulfonylureas include Glucotrol, Diabinese, DiaBeta, Micronase, Tolinase and Orinase. Sulfonylureas appear to stimulate the pancreas and increase the production of insulin from the beta cells in the pancreas. Unfortunately, there are potential unfavourable side effects from the use of sulfonylureas. Therefore, the less a patient is required to use a sulfonylurea, the fewer side effects are likely to be experienced by that patient.

Another class of hypoglycaemics are known as "biguanides". Trade-marks for some commercially available biguanides include Metformin and Glucophage. The physiological action of biguanides is not completely understood. However, biguanides may divert glucose before reaching the blood stream thereby reducing blood glucose levels. Biguanides may also increase cell receptor

sensitivity. There are potential unfavourable side effects from the use of biguanides by a patient so the less a patient uses a biguanide, the less likely the patient is to experience unfavourable side effects.

A further class of hypoglycaemics is known as the "alpha-glucosidase inhibitors". Trade-marks for some alpha-glucosdidase inhibitors include Precose, Prandase, and Acrabose. These drugs are believed to bind glucose in the gastrointestinal tract thereby reducing glucose absorption. Because there are unfavourable side effects associated with the use of alpha-glucosidase inhibitors, the less a patient uses such drugs, the less the patient is likely to experience unfavourable side effects.

The following U.S. patents are relevant to the art of orally administered insulin:

4,362,719 -	Therapeutic Method and Compositions for the Treatment of Juvenile Diabetes Mellitus
4,579,730 -	Pharmaceutical Compositions Containing Insulin
4,602,043 -	Treatment for Hypoglycemia
4,696,815 -	Anti-Diabetic Pharmaceutical Forms and the Preparation Thereof
4,708,868 -	Anti-Diabetic Pharmaceutical Forms and the Preparation Thereof
4,826,684 -	Composition for, and Method of, Treatment of Diabetes
4,849,405 -	Oral Insulin and a Method of Making the Same
4,871,739 -	Substituted 6H-7,8-dihydrothiapyrano (3,2-D)-pyrimidines as Hypoglycemic Agents
4,873,080 -	Oral Anti-Diabetic Pharmaceutical Compositions and the Preparation Thereof

4,963,526 - Oral Insulin and a Method of Making the Same

4,978,667 - Substituted 6H-7,8-dihydrothiapyrano (3,2-d)-pyrimidines as Hypoglycemic Agents

5,057,517 - Piperazinyl Derivatives of Purines and Isosteres Thereof as Hypoglycemic Agents

5,187,154 - Diagnosis and Treatment of Humans with Diabetes or at Risk to Develop Diabetes

5,206,219 - Oral Compositions of Proteinaceous Medicaments

5,234,906 - Hyperglycemic Compositions

5,284,845 - Use of Oral Diazoxide for the Treatment of Disorders in Glucose Metabolism

5,380,526 - Antidiabetic Agent and Method of Treating Diabetes

5,422,125 - Method and Composition for Treatment of Insulin Resistance Syndromes

5,424,406 - Dihydrochalcone Derivatives which are Hypoglycemic Agents

5,444,086 - Naphthalenylmethyl Thiophenones as Antihyperglycemic Agents

5,468,755 - Therapeutic Process for the Treatment of the Pathologies of Type II Diabetes

5,478,852 - Use of Thiazolidinedione Derivatives and Related Antihyperglycemic Agents in the Treatment of Impaired Glucose Tolerance in Order to Prevent or Delay the Onset of Noninsulin-Dependent Diabetes Mellitus

5,510,360 - Azolidinediones as Antihyperglycemic Agents

5,532,256 - New Azolidinediones and Thiadiazolidinediones as Antihyperglycemic Agents

5,589,183 - Method and Apparatus for Treatment of Neurogenic Diabetes Mellitus, and Other Conditions

5,595,763 - Tungsten (VI) Compositions for the Oral Treatment of Diabetes Mellitus

SUMMARY OF INVENTION

The invention is directed to a method and composition for the treatment of diabetes mellitus including Type I, IGT and Type II diabetes mellitus. More specifically, this invention pertains to a novel method of treating diabetes mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus. A therapeutic amount of insulin sensitizer can comprise one microgram to 10 grams of one or more insulin sensitizers combined or used with one or more of:

a. A therapeutically effective amount of an orally ingestible insulin which withstands degradation by passage through the stomach and upper intestine of the mammal so that a therapeutically effective level of insulin reaches the bloodstream of the mammal. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the orally ingested insulin required for a therapeutic dose, and/or,

b. An injected insulin product. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of injected insulin, and/or,

c. A sulfonylurea. The addition of the insulin sensitiz-

er is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the sulfonylurea, and/or,

d. A biguanide. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the biguanide, and/or,

e. A alpha-glucosidase inhibitor. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the alpha-glucosidase inhibitor.

The invention is directed to a method for the treatment of diabetes mellitus comprising administering to a person afflicted with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of a drug selected from the group consisting of: (a) an orally ingestible insulin; (b) an injectible insulin; (c) a sulfonylurea; (d) a biguanide; and (e) an alpha-glucosidase inhibitor.

The invention is also directed to a composition for the treatment of diabetes mellitus comprising: (a) a therapeutic amount of an insulin sensitizer; and (b) a therapeutic amount of a drug selected from the group consisting of: an orally ingestible insulin; an injectible insulin; a sulfonylurea; a biguanide; and an alpha-glucosidase inhibitor.

The method and composition can include adding a pharmaceutically acceptable carrier to the composition.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The addition of an insulin sensitizer to drugs used for the treatment of diabetes mellitus reduces the required dosage of these drugs due to the increased uptake of glucose facilitated by the insulin sensitizer.

I have discovered unexpectedly that it is possible to overcome the problem of insufficient bloodstream levels of insulin typically associated with orally ingested insulin by incorporating an orally ingestible insulin sensitizer with an orally ingestible insulin composition. While I do not wish to be bound adversely by any unsupported or invalid theories, the following description is offered as a possible explanation of why the combination of an orally ingestible insulin and an orally ingestible insulin sensitizer overcomes the problem caused by less than a therapeutic amount of insulin reaching the bloodstream when insulin is administered orally to a patient.

As discussed previously, in typical oral ingestible insulin situations to date, insufficient levels of insulin reach the bloodstream of the diabetic person because most of the insulin is destroyed in the stomach and gut of the diabetic person. However, as I have discovered, if an orally ingestible insulin sensitizer is added to the composition, and such sensitizers are not adversely affected by the strong digestive processes of the stomach and gut, the insulin sensitizer enables the lower levels of insulin that reach the bloodstream to be sufficient for purposes of enabling the cells of the body to function with the lower levels of insulin. In other words, the insulin sensitizer sensitizes the insulin insensitive cells of the body of the diabetic so that even low levels of insulin are able to attach to facilitate required glucose uptake by the

cells. Hence there is sufficient glucose uptake by the cell to enable sufficient metabolism.

My discovery is also applicable to insulin injection. When insulin is injected intravenously, in combination with an insulin sensitizer, less insulin is required to achieve the same therapeutic effect in the body. The insulin sensitizer increases the utilization of glucose at any given insulin level, so less insulin is required for an equal therapeutic result.

My discovery has application to other diabetes treatments, methods and drugs. When a sulfonylurea is used to stimulate insulin production and control diabetes mellitus, including an insulin sensitizer with the sulfonylurea, less of the sulfonylurea is required to achieve the same therapeutic effect in the body. As the amount of insulin sensitizer increases the utilization of glucose at any given insulin level, less insulin is therefore required to be manufactured by the beta cells of the pancreas for an equal therapeutic result and as a result less of the sulfonylurea may be used. Adverse side effects are reduced by lower levels of sulfonylurea.

When a biguanide is used to control diabetes mellitus, the amount of the biguanide required can be reduced and yet the same blood glucose levels in the body can be achieved when an insulin sensitizer is included with the biguanide. The insulin sensitizer increases the utilization of glucose at any given insulin level. As a biguanid reduces the amount of glucose delivered to the blood, reducing the amount of the biguanid will increase the glucose delivered to the blood which can be utilized by the body due to the addition of the insulin sensitizer. Also, adverse side effects are reduced.

My discovery can also be applied to alpha-

glucosidase inhibitors. When an alpha-glucosidase inhibitor is used to control diabetes mellitus, less of the alpha-glucosidase inhibitor is required to achieve the same blood glucose levels in the body when an insulin sensitizer is included. The insulin sensitizer increases the utilization of glucose at any given insulin level. Since an alpha-glucosidase inhibitor reduces the amount of glucose delivered to the blood, reducing the amount of the alpha-glucosidase inhibitor due to the addition of the insulin sensitizer will increase the level of glucose delivered to the blood which can be utilized by the body.

The subject compositions according to the invention can be administered parentally, topically or internally, but preferably orally, since that is the easiest form of administration. The compositions according to the invention may be formulated in any suitable orally acceptable form by employing conventional formulation techniques and conventional pharmaceutically acceptable formulation ingredients. The subject compositions according to the invention may, for example, be employed in nutritionally acceptable forms by incorporation of the compositions in a fibre supplement, a meal replacer, or a drink mix, or in pharmaceutically acceptable forms such as tablets or capsules in admixture with pharmaceutically acceptable carriers. The compositions according to the invention may also be used in combination with other pharmaceutically acceptable agents, for which the disclosed composition may be formulated in one unit with the other pharmaceutically effective agents, or in separate units administered at the same time or at separate times during a 24 hour period. The compositions according to the invention may be administered in single dosage form or in the form of subunits several times a day.

Example

G.B. - Case History

G.B. is a Type I diabetic who must normally inject insulin intravenously twice a day in order to control her Type I condition. At the suggestion of the inventor, G.B. volunteered one day to determine whether or not the addition of a small amount of an insulin sensitizer to her insulin injection would enable a lower level of insulin to be administered intravenously. At 8:30 a.m., G.B. injected intravenously her usual insulin dosage and at the same time ingested 120 mg of an oral insulin sensitizer known as V-411 (sold under the trade-mark DIAB II by Biotech Holdings Ltd.). By 11:00 a.m., the same morning, G.B. went into a hypoglycaemic state involving rapid heart beat, trembling, dizzyness and other symptoms normally associated with hypoglycaemia, a condition which G.B. was familiar with. G.B. immediately started sucking sugar cubes to endeavour to raise the sugar level in her blood and alleviate the hypoglycemic condition. However, it still took about an hour for her to stabilize her hypoglycaemic condition. The proper treatment might have been for G.B. to immediately go the emergency ward of a hospital for a glucose injection.

It was clear from G.B.'s experience with the addition of the V-411 insulin sensitizer that the effects of the insulin sensitizer were very pronounced and a normal dosage of G.B.'s normal insulin injection resulted in a condition whereby the glucose in her blood was being utilized by the cells of her body at such a high rate of efficiency that she experienced a hypoglycaemic condition. It appeared clear that there was a startling effect, and indeed perhaps a synergistic effect, created between the combination of insulin and the V-411 insulin sensitizer. Thus, much smaller dosages of insulin could have been used. Indeed, it was hypothesized that such dosages could be of

the same low level as experienced with orally administered insulin.

V-411 insulin sensitizer is known by the inventor to withstand the degradation effects of the gastric juices of the stomach and enzymatic action of the gut. Because of the strong or synergistic effect involving the combination of insulin and the insulin sensitizer, it follows that the inclusion of an insulin sensitizer in combination with an orally ingestible insulin should enable the orally ingestible insulin to work effectively in the treatment of diabetes mellitus. This is because the levels of insulin that must ultimately reach the bloodstream are greatly reduced, and such low levels are sufficient due to the effects of the insulin sensitizer.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

WHAT IS CLAIMED IS:

1. A method for the treatment of diabetes mellitus comprising administering to a person afflicted with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of a drug selected from the group consisting of:

(a) an orally ingestible insulin;

(b) an injectible insulin;

(c) a sulfonylurea;

(d) a biguanide; and

(e) an alpha-glucosidase inhibitor.

2. A method as claimed in claim 1 comprising an insulin sensitizer and an orally ingestible insulin.

3. A method as claimed in claim 1 comprising an insulin sensitizer and and injectible insulin.

4. A method as claimed in claim 1 comprising an insulin sensitizer and a sulfonylurea.

5. A method as claimed in claim 1 comprising an insulin sensitizer and a biguanide.

6. A method as claimed in claim 1 comprising an insulin sensitizer and an alpha-glucosidase inhibitor.

7. A method as claimed in claim 1 including adding a pharmaceutical carrier to the therapeutically effective amount of drug.

8. A composition for the treatment of diabetes mellitus comprising:

(a) a therapeutic amount of an insulin sensitizer; and

(b) a therapeutic amount of a drug selected from

the group consisting of: an orally ingestible insulin; an injectible insulin; a sulfonylurea; a biguanide; and an alpha-glucosidase inhibitor.

9. A composition for the treatment of diabetes mellitus in a mammal comprising:

(a) a therapeutically effective amount of an orally ingestible insulin which is formulated to withstand degradation by passage through the stomach and upper intestine of the mammal so that a therapeutically effective level of insulin reaches the bloodstream of the mammal; and,

(b) a therapeutically effective amount of one or more of a orally ingestible insulin sensitizer which withstands degradation by the stomach contents and upper intestinal tract of the mammal and reaches the bloodstream of the mammal and thereby sensitizes the cells of the mammal to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the orally ingested insulin required for a therapeutic dose.

10. A composition for the treatment of diabetes mellitus comprising:

(a) a therapeutically effective amount of an injected insulin; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of injected insulin.

11. A composition for the treatment of diabetes mellitus in a mammal comprising:

(a) a therapeutically effective amount of a sulfonylurea; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the

mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of the sulfonylurea.

12. A composition for the treatment of diabetes mellitus in a mammal comprising:

(a) a therapeutically effective amount of a - biguanide; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of the biguanide.

13. A composition for the treatment of diabetes mellitus comprising:

(a) a therapeutically effective amount of an alpha-glucosidase inhibitor; and,

(b) a therapeutically effective amount of one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of the alpha-glucosidase inhibitor.

14. A composition as claimed in claim 9 including a pharmaceutically acceptable carrier.

15. A composition as claimed in claim 10 including a pharmaceutically acceptable carrier.

16. A composition as claimed in claim 11 including a pharmaceutically acceptable carrier.

17. A composition as claimed in claim 12 including a pharmaceutically acceptable carrier.

18. A composition as claimed in claim 13 including a pharmaceutically acceptable carrier.

19. A composition as claimed in claim 9 wherein the insulin is synthetic insulin.

20. A composition as claimed in claim 10 wherein the insulin is synthetic insulin.

21. A composition as claimed in claim 9 wherein the orally ingestible insulin is present in the composition in the range of about 1 mcg to 100 mg and the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

22. A composition as claimed in claim 10 wherein the injected insulin is present in the composition in the range of about 1 mcg to 100 mg and the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

23. Any composition as claimed in claim 9 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

24. A composition as claimed in claim 10 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

25. A composition as claimed in claim 11 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

26. A composition as claimed in claim 12 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

27. A composition as claimed in claim 13 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

28. A composition as claimed in claim 8 wherein the insulin sensitizer is selected from the group consisting of BRL-49653, Pioglitazone HCL, Troglitazone, MC 555, ALRT 268, LGD 1069, Chromic Picolinate and V-411.

29. A composition as claimed in claim 12 wherein the biguanide is glucophage.

Abstract of the Disclosure

This invention is directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II). More specifically, this invention pertains to a novel method of treating diabetes mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus.

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DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the invention entitled:

METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES

which is described and claimed in:

_X_ the attached specification; or,
___ the specification in application Serial No. _____, filed _____; or,
___ as amended on _____; or,
___ PCT international application No. _____ _____ filed _____, as amended under Article 19 on _____ and/or under Article 34 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge my duty to disclose information which is material to the patentability of this invention in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed:

Prior Foreign/PCT Application(s)			Priority Claimed	
(Number)	(Country)	(Date of Filing)	Yes	No
(Number)	(Country)	(Date of Filing)	Yes	No

I claim the benefit, under 35 U.S.C. §120, of any United States application(s) or any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

U.S. Applications		Status (Check One)		
Serial No.	U.S. Filing Date	Patented	Pending	Abandoned
PCT Applications Designating US				
PCT No.	Filing Date	USSN		

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

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Title: **METHOD AND COMPOSITION FOR THE TREATMENT OF DIABETES**

Filed: Herewith

Date: 20 February, 1997

To: Assistant Commissioner for Patents
Washington, D.C.
20231

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ASSOCIATE POWER OF ATTORNEY

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